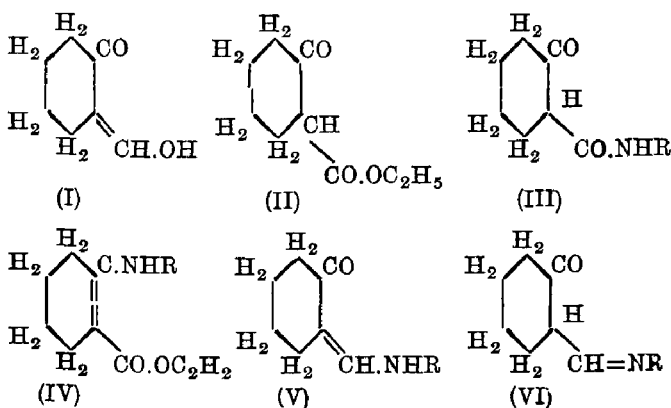


**Formation of Heterocyclic Compounds. Part IV.**  
**Interaction of Ethyl *cyclo*Hexanone-2-carboxylate with**  
**Arylamines. Part I. Synthesis of Tetrahydro-**  
**phenanthridones.**

BY HEMENDRA KUMAR SEN AND UMAPRASANNA BASU.

In a previous communication by one of us (Sen and Mondal, *J. Indian Chem. Soc.*, 1928, 5, 609) it was shown that the generally accepted notion of hydroxymethylene ketones being permanently enolised  $\beta$ -diketones, cannot be held as being strictly correct. Even their sodium salts have been found capable of reacting with alkyl iodides in both phases (*loc. cit.*). While interesting results are expected from a study of the intensities of absorption in keto-enol equilibria, it was found necessary for the purpose of our work to establish a reasonable chemical difference between  $\beta$ -diketones and hydroxymethylene ketones in condensation reactions, although the inherent defect of the chemical method of handling equilibrium mixtures cannot but be recognised.

In the present investigation the behaviour of ethyl *cyclo*hexanone-2-carboxylate (II) with aniline and substituted anilines has been studied. It is obvious that there are two centres of reaction with aniline both in (I) and (II), namely at the acid part as also at the ketonic group. In the case of (II), the reaction of aniline at the ester part would invariably give rise to an anilide (III), whilst in the case of (I), both anilide (V) and anil (VI) may be formed:—



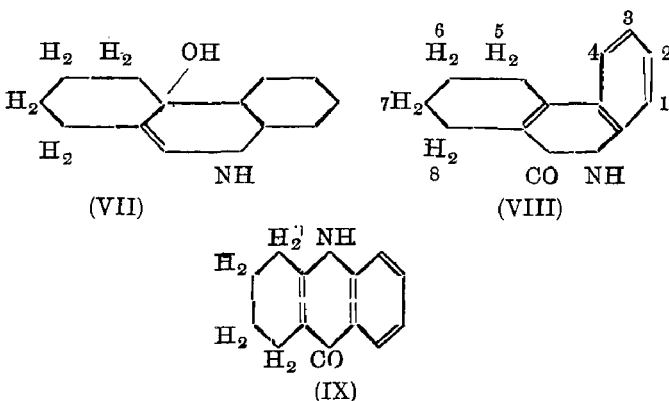
R=An aryl group.

A comparison of the absorption spectra of the compound obtained by the interaction of aniline and hydroxymethylene cyclohexanone with those of the aniline and anil of cyclohexanone carboxylate, showed that the hydroxymethylene derivative is distinctly analogous to the anil (IV). Further study in this direction is in progress.

Whilst the anilides (III) of the keto-ester gave a violet coloration with alcoholic ferric chloride, neither the anil (IV) of the ester nor the aniline derivative of the hydroxymethylene cyclohexanone gave any coloration. This behaviour can be explained from their respective structural formulæ. It would be noticed that neither in (IV) nor in (V) there is any labile hydrogen atom to enolise a keto group which is at the bottom of ferric chloride reaction. This is further corroborated by the fact that the amount of absorption is far more in (III) than in (IV) and (V) as should be expected from the enolic structure of (III). Besides, the *ortho*-quinonoid structure of (V) would require it to be coloured. As a matter of fact, it is a bright yellow compound whereas (IV) is almost colorless.

The direct consequence of the absence of enolising hydrogen in (V) may account for its inability to form ring compounds under the influence of sulphuric acid. Repeated attempts to prepare (VII) failed in our hands (*cf.* Borsche, *Annalen*, 1910, 377, 70).\*

On the other hand, the anilide (III) of ethyl cyclohexanone-2-carboxylate, on being heated with concentrated sulphuric acid for a short time, gives a good yield of the 5:6:7:8-tetrahydrophenanthridone derivative (VIII).



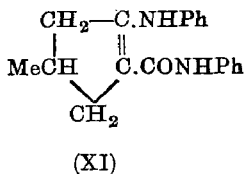
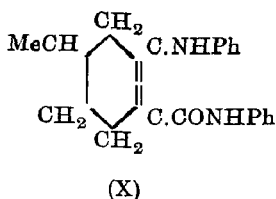
\*Thielepape (*Ber.*, 1922, 55, 131), however, records two cases where in spite of the presence of enolising hydrogen, ring closure could not be effected. In the light of the present work, his experiments need repetition.

As the tetrahydrophenanthridones form a new class of compounds, they were synthesised from various anilides of ethyl cyclohexanone-2-carboxylate. As a  $\beta$ -ketonic ester, ethyl cyclohexanone 2-carboxylate may react in two ways giving rise to either (III) or (IV) (cf. Conrad and Limpach, *Ber.*, 1887, 20, 944; 1891, 24, 2990; Knorr, *Ber.*, 1883, 16, 2593; 1884, 17, 540; 1887, 20, 1397; *Annalen*, 1886, 236, 69; 1888, 245, 378; Knorr and Reuter, *Ber.*, 1894, 27, 1169; Besthorn and Garben, *Ber.*, 1900, 33, 3439; Dieckmann, *Annalen*, 1901, 317, 91; Ewins and King, *J. Chem. Soc.*, 1913, 103, 104; Thielepape, *Ber.*, 1922, 55, 131. In order to obtain pure products on the one hand, and products of known constitution on the other, the first step in this syntheses was to know the constitution of the products of the reaction with the amines definitely. An anil (IV) would give rise to a tetrahydroacridone derivative (IX) whereas an anilide (III) would yield tetrahydrophenanthridone (VIII).

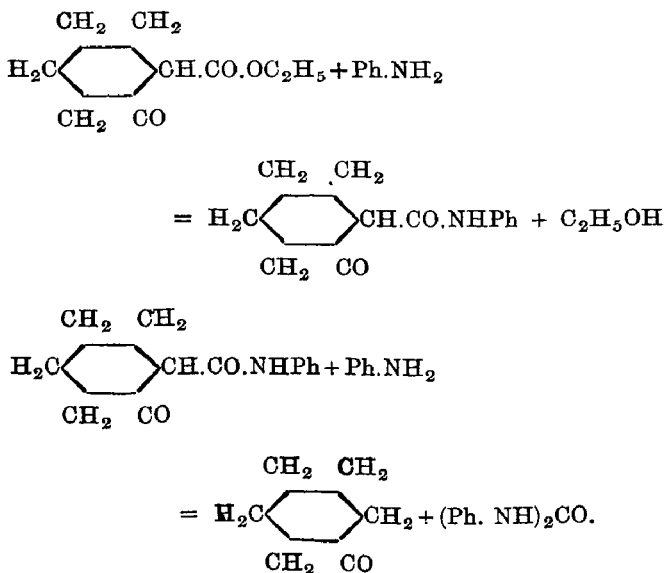
On heating ethyl cyclohexanone-2-carboxylate (1 mol.) with a primary arylamine (1 mol.) at 190-200° for periods varying from 2 to 30 minutes at first a solid product is isolated which on purification gives a violet coloration with an alcoholic solution of ferric chloride indicating thereby the presence of an enolic group and as such pointing to the anilide (and not anil) constitution of the product. The other reason which has lead us to the conclusion that this reaction product is an anilide, is that the compound when dissolved in concentrated sulphuric acid and heated for 20 minutes on a water-bath, is transformed into a tetrahydrophenanthridone derivative. The corresponding isomeric compound tetrahydro-acridone is known and described by Tiedtke (*Ber.*, 1909, 42, 631) as colorless needles, m.p. 258°. Our compound obtained from ethyl cyclohexanone-2-carboxylate-anilide crystallises in fine prismatic needles melting at 273°. It would be important now to distil it with zinc dust to obtain phenanthridine itself. This will be undertaken as soon as the quantity of material permits.

It may be mentioned here that many years ago Kötze and Merkel (*J. pr. Chem.*, 1909, (ii), 79, 102) succeeded in transforming ethyl 5-methyl-cyclohexanone-2 carboxylate into its anilino-anilide derivative (X) by boiling it with aniline. These authors also heated ethyl cyclohexanone-2-carboxylate with aniline and obtained a compound which they described as ethyl 2-anilido- $\Delta^1$ -cyclohexene-1-carboxylate (IV, R=Ph) melting at 29°. Reference may be made in this connection to a compound described by Dieckmann (*loc. cit.*) which he

obtained by heating ethyl 4-methyl-cyclopentanone-2-carboxylate with aniline (2 mols.) and described it as an anilino-anilide (XI).



But by working under the conditions described in the experimental portion of this paper, no such compound was isolated whether the ester was allowed to react with 2 mols. of aniline or with one molecule. If instead of equimolecular proportions of the keto-ester and a primary amine, 2 molecules of the latter and one molecule of the former are heated above  $150^\circ$  for several hours, the product separating from the liquid is a diaryl carbamide derivative whilst the mother-liquor retains the anilide similar and identical in properties to the anilides obtained in other ways. The yield of the carbamide derivative varies between 30 and 50 per cent. of the weight of the amine used (*cf.* Oppenheim and Precht, *Ber.*, 1876, 9, 1098). The reaction in our case may be expressed as below:—



In our experiments, the simultaneous formation of the carbamide derivative and the anilide would point to the conversion of the latter into the former, a view also held by Knorr (*Annalen*, 1836, 236, 69) who isolated diaryl carbamides by distilling the anilides.

All the tetrahydro-phenanthridones, described in this paper, are crystalline solids of high melting points. They are insoluble in alkali but dissolve in concentrated sulphuric acid giving colorless solutions without fluorescence, from which they are again precipitated on dilution with water.

Whilst generally high temperatures give rise to anilides, the interaction of the keto-ester and the aryl amines at ordinary temperature yields the corresponding anils.\* Thus *p*-amino-acetanilide when reacted with the keto-ester in acetic acid solution yields a well crystalline product which imparts no coloration to alcoholic ferric chloride. This fact and the analytical result prove it to be an anil. Similarly by reacting the keto-ester with aniline, a product has been isolated which melts at 57.5° and does not give any coloration with alcoholic solution of ferric chloride. This is also provisionally accepted as an anil. Further work to prove its constitution by converting it into known tetrahydro-acridone (IX) (*loc. cit.*) is in progress.

#### EXPERIMENTAL.

##### *Ethyl cycloHexanone-2-carboxylate and Aniline.*

(i) *Formation of cycloHexanone-2-carboxylate-anilide.* (Formula III, R=Ph).—Ethyl cyclohexanone-2-carboxylate (4 g.) and aniline (2.2 g.) were heated under reflux at 185° for about half an hour in an oil-bath. The mass after reaction was washed with dilute hydrochloric acid and taken up in ether. The ethereal solution, on drying and evaporating, left a viscous liquid which, after several washings with petroleum ether, yielded a granular solid. The substance was crystallised by dissolving in ether and diluting the solution with petroleum ether in which solvent the compound was insoluble. (Found: N, 6.72. C<sub>13</sub>H<sub>15</sub>O<sub>2</sub>N requires N, 6.45 per cent.).

It melts at 104-105° and is soluble in most organic solvents and to some extent in warm water, but it is insoluble even in strong

\* The reaction between aniline and methyl benzoylacetate at 150°, however, for a long time gives rise to a mixture of  $\beta$ -phenylamidophenylacrylic anilide (NHPh, CPh:CH.CO.NHPh) and benzoylactic anilide (Ph.CO.CH<sub>2</sub>.CONHPh). (Knorr, *Annalen*, 1888, 245, 378).

caustic soda solution. In alcoholic solution it gives with ferric chloride a fine violet coloration. The anilide when heated with concentrated sulphuric acid for a few minutes on a water-bath, yields tetrahydrophenanthridone (described below) on pouring the acid solution into water.

(ii) *Formation of Diphenylcarbamide*.—A mixture of ethyl cyclohexanone-2-carboxylate (2 g.) and aniline (2.2 g.) was heated under reflux on an oil-bath for 7 to 8 hours at 150-160°. Next day fine needles (1.1 g.) were collected. These crystallised from rectified spirit in flaky needles, m. p. 235°. (Found: N, 13.32.  $C_{13}H_{12}ON_2$  requires N, 13.21 per cent.).

The identity of the compound was established by taking a mixed melting point with diphenylcarbamide.

(iii) *Formation of 5:6:7:8-Tetrahydrophenanthridone* (VIII).—The ester and aniline were heated in molecular proportion at 190° for an hour. The liquid was then repeatedly washed with dilute hydrochloric acid and then with petroleum ether for several times. A viscous liquid was left behind. Without isolating the substance, it was treated with concentrated sulphuric acid for 20 minutes at the temperature of the boiling water-bath. The red solution was poured into water when a white solid was obtained. It crystallises from glacial acetic acid, diluted with a few drops of water, in fine prismatic needles melting at 273°. (Found: N, 7.07.  $C_{13}H_{13}ON$  requires N, 7.03 per cent.).

The substance is insoluble in alkali but dissolves in concentrated sulphuric acid forming a colorless solution without fluorescence, from which it is precipitated unchanged on dilution with water. Its isomeric compound tetrahydroacridone (IX) was also prepared by heating cyclohexanone with anthranilic acid according to the method of Tiedtke (*loc. cit.*). A mixture of this and our compound melted at 255°.

*Ethyl cycloHexanone-2-carboxylate and p-Toluidine.*

(i) *Formation of Di-p-tolylcarbamide*.—The ester (2 g.) and p-toluidine (2.5 g.) were heated together for 7 hours at 160°, the carbamide derivative separating after 3 hours' heating (yield, 1 gm.). It crystallises from rectified spirit in flakes melting at 260°. (Found: N, 11.88.  $C_{15}H_{16}ON_2$  requires N, 11.66 per cent.).

(ii) *Formation of cycloHexanone-2-carboxylate-p-toluidide*. (Formula III, R = p-Tol).—The di-p-tolylcarbamide obtained by heating a mixture of the ester (2 g.) and p-toluidine (2.5 g.) at 160° for 3

hours was filtered off. The mother-liquor was then washed with dilute hydrochloric acid, and on scratching the residual liquid, a solid was obtained. This was filtered and washed with petroleum ether and dried. Its ethereal solution being once treated with animal charcoal was allowed to evaporate. The crystals thus obtained were washed with petroleum ether when they melted at 108-109°. (Found: N, 6.46,  $C_{14}H_{17}O_2N$ , requires N, 6.06 per cent.).

The substance is insoluble in alkali; in an alcoholic solution, it gives with ferric chloride a violet coloration.

(iii) *Formation of 3-Methyl-5:6:7:8-tetrahydrophenanthridone.*—A molecular proportion of the ester (2 g.) was mixed with the molecular proportion of *p*-toluidine (1.25 g.) and the mixture was heated for 2 minutes at 192-193° on an oil-bath. The red liquid obtained was washed with dilute hydrochloric acid when, on scratching, a solid was isolated. It was filtered, dried and washed with petroleum ether. The substance thus obtained (1.1 g.) on crystallisation melted at 108°. The mixed m.p. of this with that previously obtained was also 108°. It gave the usual color reaction with ferric chloride and was insoluble in alkali.

The toluidide thus obtained was dissolved in concentrated sulphuric acid (3 c.c.) and the solution was heated on a boiling water-bath for 20 minutes, and then poured into water (40 c.c.) when a white crystalline solid separated out. The yield was quantitative. The substance crystallises from glacial acetic acid diluted with water in fine prismatic needles, melting at 286-288°. (Found: N, 6.68.  $C_{14}H_{15}ON$  requires N, 6.57 per cent.).

The compound gives no color reaction with ferric chloride and is insoluble in alkali but dissolves in concentrated sulphuric acid forming a colorless solution without fluorescence.

*Ethyl cycloHexanone-2-carboxylate and m-Xylidine (asymmetric).*

(i) *Formation of Di-m-xylidylcarbamide.*—A mixture of the ester (2 g.) and xylidine (2.8 g.) was heated for 4½ hours at 180° when about 1 g. of the condensation product was obtained. The carbamide began to separate after 1½ hours' heating. Crystallising from alcohol it melted at 262°. (Found: N, 10.65,  $C_{17}H_{20}ON_2$  requires N, 10.45 per cent.).

(ii) *Formation of cycloHexanone-2-carboxylate-m-xylidide.*—A mixture of the ester (4 g.) and xylidine (5.7 g.) was heated under reflux for 4½ hours at 170-180°. The solid separated was filtered

off. The filtrate was washed with dilute acid when on scratching the residual liquid a solid was isolated. It was collected and washed with petroleum ether. Yield 2 gms. It was crystallised from methyl alcohol with the addition of animal charcoal. Recrystallised from the same solvent with a few drops of water, it melted at 125-126°. (Found: N, 5.88.  $C_{15}H_{19}O_2N$  requires N, 5.71 per cent.).

This xylidide is a well crystallised substance, insoluble in alkali and alkaline carbonate; on boiling the solution, however, the substance goes readily into solution in the former but with difficulty in the latter. In alcoholic solution it gives with ferric chloride a violet coloration.

(iii) *Formation of 1:3-Dimethyl-5:6:7:8-tetrahydrophenanthridone.*—A mixture of ester (2 g.) and the xylidine (1.42 g.) was rapidly heated up to 200° for 2 minutes. On cooling a solid mass was obtained. It was washed with dilute hydrochloric acid and then with petroleum ether (yield, 1 g.). It melted at 123°. The mixed m.p. of it with the anilide previously obtained is 124-125°.

The anilide (1 g.) on usual treatment with sulphuric acid gave 0.9 gm. of the phenanthridone, m.p. 270-71° (from glacial acetic acid). (Found: N, 6.29.  $C_{15}H_{17}ON$  requires N, 6.17 per cent.).

The substance is soluble in concentrated sulphuric acid without any coloration and fluorescence.

*Ethyl cycloHexanone-2-carboxylate and  $\beta$ -Naphthylamine.*

(i) *Formation of Di- $\beta$ -naphthylcarbamide.*—The ester (2 g.) was heated with  $\beta$ -naphthylamine (3.3 g.) at 170° for three hours. The crystals separated were filtered off and washed with ether. Yield 0.8 gm. The expected  $\beta$ -dinaphthylcarbamide was crystallised from amyl acetate when it melted at 301-302°.

(ii) *Formation of cycloHexanone-2-carboxylate- $\beta$ -naphthylamide.*—The filtrate from the above reaction was treated with dilute hydrochloric acid and the solid (2.5 g.) separated was collected. It was washed with petroleum ether and crystallised from alcohol using animal charcoal. Recrystallised from the same solvent, it melted at 149°. (Found: N, 5.38.  $C_{17}H_{17}O_2N$  requires N, 5.24 per cent.).

It is insoluble in sodium carbonate solution, and in alcoholic solution it gives with ferric chloride the usual violet coloration.

(iii) *Formation of 3:4-Benzo-5:6:7:8-tetrahydrophenanthridone.*—A mixture of the ester (2 g.) and  $\beta$ -naphthylamine (1.7 g.)



was heated at 205° for 2 minutes. The viscous mass obtained was repeatedly washed with hot benzene when about 1.1 g. of the substance (m.p. 145°) were obtained. The mixed m.p. with that previously obtained was 148-149°. It also gave the usual chemical reactions.

From 1 gm. of this substance 3:4-benzo-5:6:7:8-tetrahydrophenanthridone was obtained by the usual method (yield, 0.7 gm.). It crystallises from glacial acetic acid diluted with a few drops of water; m.p. 291°-292°. (Found: N, 5.70.  $C_{17}H_{15}ON$  requires N, 5.62 per cent.).

*Ethyl cycloHexanone-2-carboxylate and  $\alpha$ -Naphthylamine.*

(i) *Formation of Di- $\alpha$ -naphthylcarbamide.*—The ester (2 g.) and the amine (3.4 g.) were heated together at 170-180° for 3 hours, the solid separating even after half an hour. The mass was cooled and repeatedly washed with boiling alcohol to remove any unchanged  $\alpha$ -naphthylamine. The residue was crystallised from amyl acetate in which di- $\alpha$ -naphthylcarbamide was somewhat soluble. It melted at 288°. (Found: N, 9.17.  $C_{21}H_{16}ON_2$  requires N, 8.97 per cent.).

*Ethyl cycloHexanone-2-carboxylate and p-Aminoacetanilide.*

(i) *Formation of cycloHexanone-2-carboxylate-p-acetamidoanilide.* (Formula III,  $R = \cdot C_6H_4NHAc$  (para).—A mixture of the keto-ester (4 g.) and *p*-aminoacetanilide (3.6 g.) was heated at 185-190° for about half an hour when a thick sludge was obtained. On rubbing the mass with dilute hydrochloric acid, a solid (about 3.6 gm.) was isolated. It crystallises from dilute alcohol in fine crystals melting at 182.5°. (Found: N, 10.04.  $C_{15}H_{18}O_3N_2$  requires N, 10.2 per cent.).

The substance is soluble in boiling caustic soda solution and gives with ferric chloride in alcoholic solution the characteristic violet coloration of the anilides. Here it should be noticed that the first product separating from the reaction mixture is the anilide itself and the yield is about 55-60 per cent. of the theory.

(ii) *Formation of Ethyl 2-p-Acetamidoanilido- $\Delta^1$ -cyclohexene-1-carboxylate.* (Formula IV,  $R = \cdot C_6H_4.NHAc$  (para).—Molecular proportions of the keto-ester and *p*-aminoacetanilide were taken in glacial acetic acid solution and the flask being corked was left overnight. Next day a beautiful crystalline compound was found. This was collected and the mother-liquor, on concentration and afterwards dilution with water, gave another crop of the same

substance (total yield, about 40 per cent.). The substance crystallises from alcohol in small glistening flakes. As the substance and the solution were found to be colored, the latter was twice treated with animal charcoal, but the final product still retained a light yellow tinge. (Found: N, 9.5.  $C_{17}H_{23}O_3N_2$  requires N, 9.27 per cent.).

This compound melts at  $191.5^\circ$ , and imparts no coloration to alcoholic ferric chloride. A mixture of this with the anilide (m.p.  $182.5^\circ$ ) melted at  $159^\circ$ .

*Ethyl cycloHexanone-2-carboxylate and Aniline.*

(i) *Formation of Ethyl 2-Anilido- $\Delta^1$ -cyclohexene-1-carboxylate* (IV, R=Ph).—The keto-ester (8 g.) and the aniline (4.4 g.) were mixed together and left overnight. Next day the mixture was found to be turbid owing to the separation of water. The flask was left for 3 days in a vacuum over fused calcium chloride. Fine crystalline solid began to separate. After a week the contents set to a hard mass which was collected and dried over porous plate (10.5 gm.). It crystallises from methyl alcohol in prisms with a very light yellow tinge and melts at  $57.5^\circ$  (sharp). The mixed m.p. with the corresponding anilide previously obtained was  $54^\circ$ . It gives no coloration with alcoholic ferric chloride. It dissolves in ether, alcohol and even in petroleum ether in which the corresponding anilide is insoluble.

The compound is provisionally regarded as a compound similar to that described by Kötze and Merkel (*loc. cit.*) who, however, recorded a melting point of  $29^\circ$ .